low doses of penicillin, therefore, can be attributed to unusual characteristics of invasive gonococci. Recurrent neisserial bacteremia should alert physicians to a genetic deficiency in terminal complement components. Immunization to improve killing of resistant gonococci in the blood is a promising approach to prevention of DGI.

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Clinically Applicable Radioimmunoassays of Parathyroid Hormone

BOTH INTACT 84-amino-acid biologically active parathyroid hormone (PTH 1-84) and biologically inactive carboxyl-terminal ("C") fragments of PTH 1-84 circulate in human blood. The "C" fragments are derived both from the parathyroid glands and from the peripheral metabolism of PTH 1-84. Their concentration in the peripheral blood is relatively higher than PTH 1-84 because they survive longer in the circulation.

Serum radioimmunoassays (RIA) of PTH using antisera that react well with circulating "C" fragments ("C" assays) distinguish normal from hyperparathyroid subjects better than assays that detect only PTH 1-84. RIA's using antisera that react only with intact PTH 1-84 ("I" assays) are better in showing step-up differences between peripheral serum immunoreactive PTH (iPTH) and iPTH in serum draining parathyroid tumors.

All generally available RIA's of PTH have been developed with nonhuman reagents. Likewise, their ability to detect intact (amino terminal) or carboxyl terminal PTH have been determined with fragments of bovine PTH. Such studies do not adequately characterize the specificity of assays for *human* PTH. Fragments of human PTH are not commercially available.

At present, the only (and probably the best) way to characterize RIA's to be used for diagnostic purposes in humans is to determine the species of iPTH circulating in human peripheral serum recognized by a given RIA. This can be done easily by measuring the iPTH in the effluent fractions of gel-filtered hyperparathyroid serum and this information should be available to the user. Therefore, assuming adequate sensitivity, RIA's which recognize both intact PTH 1-84 and the larger molecular weight carboxyl terminal fragments of PTH in hyperparathyroid serum are "C" assays and can be expected to provide excellent discrimination between normal subjects and patients with hyperparathyroidism. RIA's which recognize primarily intact PTH can be expected to give the greatest step-up differences between peripheral and parathyroid venous effluent serum obtained during parathyroid localization procedures.

Selecting an appropriate RIA of PTH for diagnostic application has become a difficult and somewhat exasperating chore for most physicians because of the exponential growth in the number of assays available and competition-induced claims of advantages of one assay over another. The simple criteria given in this epitome for selecting clinically applicable RIA's for PTH should be helpful in making objective choices.

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Hepatotoxicity Caused by Acetaminophen or Salicylates

ACUTE ACETAMINOPHEN OVERDOSAGE may result in massive hepatic necrosis with encephalopathy and death. Toxicity is mediated by an oxidized metabolite of acetaminophen that depletes intracellular glutathione levels. Generally, single doses in excess of 15 grams are required, although severe liver damage has occurred with ingestion of 10 grams in the presence of alcohol or drugs that induce the microsomal enzymes. Therapeutic dosages consumed for several weeks may also cause hepatitis with elevation of the serum transamines, alkaline phosphatase and bilirubin; centrilobular necrosis may occur. As little as 3 grams a day may be hepatotoxic, although injury seems more common at levels of 5 to 8 grams per day. The inflammation and necrosis are reversible on cessation of the drug, and no cases of cirrhosis have been reported with either acute overdosage or chronic ingestion.

Unlike acetaminophen, acute salicylate intoxication does not result in hepatic necrosis. Chronic ingestion of salicylates, however, in patients with acute rheumatic fever, juvenile rheumatoid arthritis, systemic lupus erythematosus or Reiter syn-

drome may lead to elevation of hepatic enzymes. Toxicity is unusual at serum salicylate levels of less than 20 mg per dl, but in one series toxicity occurred in all patients with juvenile rheumatoid arthritis in whom levels were greater than 25 mg per dl. Liver biopsy studies show a mononuclear cell infiltrate of the portal triads with scattered cellular necrosis that occasionally is consistent with chronic active hepatitis. As with acetaminophen, the toxicity is reversible. Lower dosages can be reinstituted providing the hepatic enzymes and serum salicylate level are monitored closely.

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Cimetidine in the Treatment of Peptic Ulcer Disease

A NEW CLASS of compounds, termed the histamine type 2 or H-2 receptor antagonists, has been added to the ever-expanding list of drugs used in the treatment of acid peptic ulcer disease. Cimetidine, the only H-2 antagonist currently available in the United States, has undergone extensive basic research testing and clinical trials documenting its ability to profoundly decrease gastric acid secretion. Histamine receptors on the gastric parietal cell playing an important role in the stimulation of hydrochloric acid secretion through all modalities (cephalic phase by vagal innervation, stimulated by food and stimulated by gastrin) are not antagonized by the traditional antihistamines (called H-1 receptor antagonists) such as diphenhydramine (Benadryl®). The H-2 receptor antagonists, such as cimetidine, block to a major degree the acid output stimulated by all known gastric secretagogues.

Early H-2 receptor antagonists, particularly metiamide, were found in some clinical trials to be associated with neutropenia on rare occasions. However, no significant toxicity has been found with cimetidine use, although isolated reports of gynecomastia have appeared. Cimetidine cannot yet be recommended to pregnant or nursing women.

Cimetidine has been shown to be effective in healing duodenal ulcers. Gastric acid secretion and acid delivery to the duodenum are significantly reduced with cimetidine therapy and it is associated with an improved rate of ulcer healing. Studies are in progress assessing the efficacy of cimetidine therapy in gastritis and gastric ulceration, as well as the prophylactic usefulness of continuous long-term nocturnal cimetidine administration for acid peptic disease.

Cimetidine usage should be considered in patients with gastric acid hypersecretory states such as Zollinger-Ellison syndrome and systemic mastocytosis and in patients who cannot or will not take effective doses of antacids for duodenal ulcer disease. The oral dosage is one 300 mg tablet with each meal and an additional 300 mg at bedtime. A parenterally administered form is available for patients who cannot take orally given medication. The drug should be administered in these latter patients in a dosage of 300 mg (mixed with 100 ml of a 5 percent dextrose solution) every six hours. The drug should not be used for dyspepsia without documented duodenal ulceration and it should be used with caution in patients with routine duodenal ulcers. With this drug, as with all new drugs, practicing physicians must be alert to unusual, unreported manifestations of toxicity.

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Pituitary Cushing Syndrome: New Options for Treatment

HYPERCORTISOLISM in two thirds of all cases is secondary to excessive secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland (pituitary Cushing syndrome). The mainstay of treatment for more than three decades has been total bilateral adrenalectomy. This treatment has brought its own problems including a significant mortality rate, persistent or recurrent hypercortisolism due to hyperplastic remnant or ectopic adrenal tissue, postoperative pituitary tumors (Nelson syndrome) and, almost invariably, lifelong dependence upon replacement therapy with adrenocortical hormones. Recent therapeutic advances now offer promise of making total adrenalectomy obsolete over the next few years.

Pituitary radiation has been used with limited success as a primary treatment in adults, perhaps